

[ CASE REPORT ]

## Lipoprotein Lipase Deficiency Arising in Type V Dyslipidemia

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### Abstract:

A 40-year-old Japanese man presented with child-onset hypertriglyceridemia recently complicated by diabetes mellitus. The patient's diabetes mellitus was maintained, but he had persistent insulin resistance. The patient also had persistent severe hypertriglyceridemia (1,224-4,104 mg/dL), despite the administration of bezafibrate and ezetimibe. Type V dyslipidemia was revealed by agarose gel electrophoresis and the refrigerator test, and a significantly reduced post-heparin lipoprotein lipase mass of 26 ng/mL was confirmed. Genetic testing confirmed two heterozygous *LPL* variants, p.Tyr88X and p.Gly215Glu in trans; thus, the patient was diagnosed with lipoprotein lipase deficiency. Lipoprotein lipase deficiency typically arises in type I dyslipidemia, but is latent in type V dyslipidemia.

**Key words:** lipoprotein lipase, chylomicronemia, triglycerides

(Intern Med 58: 251-257, 2019)

(DOI: 10.2169/internalmedicine.0952-18)

### Introduction

Primary chylomicronemia is a metabolic disease characterized by severe hypertriglyceridemia due to the presence of chylomicrons in the plasma even after a 12-14-hour fast. The genetic etiology is roughly classified into two groups: monogenic and polygenic chylomicronemia (1). Monogenic chylomicronemia is also known as familial chylomicronemia, which typically occurs in childhood to adolescence with an autosomal recessive pattern of inheritance and which is associated with the severe accumulation of chylomicrons, and conditions such as eruptive xanthoma, lipemia retinalis, hepatosplenomegaly and sometimes recurrent pancreatitis, which is a leading cause of mortality in patients with the disease (1, 2). Bi-allelic pathogenic variants in genes encoding key proteins for the lipolysis cascade, *LPL*, *APOC2*, *APOA5*, *GPIHBP1* and *LMF1*, are now widely accepted as the genetic etiology of monogenic chylomicronemia (1, 2). Because the effect of pharmacological treatment is very limited, a low-fat diet is the mainstay of treatment for patients with monogenic chylomicronemia (1, 3). In contrast, polygenic chylomicronemia occurs in adulthood with a

genetic background, which can include rare heterozygous variants with a large effect on causative genes for monogenic chylomicronemia and the accumulation of common variants associated with hypertriglyceridemia in the wake of secondary factors such as obesity, diabetes mellitus, alcohol intake, pregnancy or some drugs, including those for humoral therapy (1, 3). In these patients, the clinical manifestations are milder and the risk of pancreatitis is relatively low in comparison with monogenic chylomicronemia. Furthermore, fibrate can reduce the serum triglyceride (TG) level and the risk of acute pancreatitis (4). Thus, in managing patients with primary chylomicronemia, gene sequencing is an important diagnostic process because the pharmacological response, susceptibility to pancreatitis and effects on the next generation depend on the underlying genetic etiology. In this article, we discuss a newly diagnosed case of monogenic chylomicronemia due to lipoprotein lipase (LPL) deficiency occurring as a consequence of compound heterozygous *LPL* variants p.Tyr88X and p.Gly215Glu.

## Case Report

### Patient

A 40-year-old Japanese man was referred to our hospital for further investigation of severe fasting hypertriglyceridemia (serum TG level: 1,434 mg/dL). Hypertriglyceridemia with creamy serum was initially noted at 5 years of age in an examination to determine the cause of intermittent abdominal pain after the consumption of a high-fat diet. The patient was advised to restrict his fat intake, but there was no follow-up and the patient did not undergo routine medical check-ups after the diagnosis. A history of acute pancreatitis was not apparent. At 39 years of age, severe hypertriglyceridemia with serum that had a milky appearance, hypertension and diabetes mellitus were evident at the patient's first medical examination as an adult. The patient's diabetes mellitus was uneventfully maintained by caloric restriction with a low-fat diet, exercise and sitagliptin (100 mg, once daily). A recent examination revealed the following findings: fasting plasma glucose, 137 mg/dL; fasting C-peptide, 2.1 ng/mL; glycosylated hemoglobin, 6.6%; and urinary albumin to creatinine ratio, 87.8 mg/g creatinine. The patient's hypertension was satisfactorily controlled with olmesartan (20 mg, once daily) and azelnidipine (16 mg, once daily).

The patient rarely consumed alcohol and took no medicines other than sitagliptin, olmesartan and azelnidipine. His family history included no coronary artery disease. The patient's paternal and maternal grandmothers both had hypertriglyceridemia and the patient's father had hypertriglyceridemia and diabetes mellitus; however, there was no apparent history of chylomicronemia or acute pancreatitis. A detailed biochemistry examination was not possible because these individuals were deceased. His mother did not have hypertriglyceridemia but did have hypercholesterolemia, which was being treated with diet therapy at another hospital. Although the patient's elder sister, who was 45 years of age, was not obese (body mass index, 19.6 kg/m<sup>2</sup>; height, 148 cm; weight, 43 kg) and was not pregnant, she had chylomicronemia resulting in severe hypertriglyceridemia. Recent tests at another hospital revealed the following findings: TG, 1,804 mg/dL; total cholesterol (TC), 244 mg/dL; high-density lipoprotein cholesterol (HDL-C), 13 mg/dL and low-density lipoprotein cholesterol (LDL-C), 38 mg/dL. She had experienced acute pancreatitis at 39 years of age. The patient's sister lived too far away for us to perform blood tests or a physical examination.

A physical examination revealed the following: body mass index, 24.4 kg/m<sup>2</sup> (height, 162 cm; weight, 64 kg); waist circumference, 88 cm; and blood pressure, 118/82 mmHg, with a regular pulse of 96 beats/min. Hepatosplenomegaly was observed but neither lipemia retinalis nor skin stigmata (including eruptive xanthoma) was apparent. Careful inspection and palpation did not reveal Achilles' tendon thickening. There were no remarkable findings of the

head, neck, chest or extremities. Abdominal ultrasonography revealed no remarkable findings with regard to the pancreas; however, a spleen index of 62.4 cm<sup>2</sup> and enlargement of the liver with a smooth surface, dull edges, high echogenicity, deep attenuation and vascular blurring were confirmed.

Bezafibrate (200 mg, twice daily) and ezetimibe (10 mg, once daily) were administered in addition to fat restriction; however, the patient's fasting serum TG level (minimum, 1,224 mg/dL; maximum, 4,104 mg/dL) remained markedly high.

### Evaluation of lipids and apolipoproteins, performance of agarose gel electrophoresis and the refrigerator test, and determination of the pre- and post-heparin LPL mass

A blood sample was obtained from the patient after an overnight fast [with the continuation of bezafibrate (200 mg, twice daily) and ezetimibe (10 mg, once daily)]. Serum fraction was isolated from whole blood and used for assays of lipids and apolipoprotein and the performance of agarose gel electrophoresis and the refrigerator test. TC, TG and HDL-C levels were measured by an enzymatic technique and a direct method using a Cobas 8000 modular analyzer (Roche Diagnostics, Basel, Switzerland). LDL-C was directly measured using a LABOSPECT 008 auto-analyzer (Hitachi, Tokyo, Japan). Apolipoprotein (apo) A-I, apoA-II, apoB, apoC-II, apoC-III and apoE were measured by immunonephelometry using a JCM-BM 8000 series instrument (JOEL, Tokyo, Japan). ApoE phenotype was determined using a Phenotyping Apo E kit (JOKOH, Tokyo, Japan). Agarose gel electrophoresis was performed using QuickGel LIPO (Helena Laboratories, Saitama, Japan) on Epalyzer2 automated electrophoresis equipment (Helena Laboratories). The serum appearance was examined after overnight refrigeration at 4°C. Using a plasma fraction isolated from whole blood, the pre-heparin LPL mass was determined using a LPL Elisa Daiichi kit (Sekisui Medical, Tokyo, Japan). Subsequently, another blood sample was obtained 15 minutes after the intravenous injection of 30 units/kg heparin. The post-heparin LPL mass was determined using the plasma fraction isolated from whole blood.

### Whole exome sequencing and Sanger confirmation

Genomic DNA was isolated from blood samples using the Wizard Genomic DNA Purification Kit (Promega, Madison, USA). Exon capture was performed using a SureSelect Human V6-post (Agilent Technologies, Santa Clara, USA), and whole exome sequencing was performed on a HiSeq4000 (Illumina, San Diego, USA). Sequences were mapped to reference data using a Burrows-Wheeler Aligner 0.7.12 (<http://bio-bwa.sourceforge.net>). UCSC Hg19 (<https://genome.ucsc.edu>) was used for the reference sequence. Variants were identified using Genome Analysis Toolkit v3.4.0 (<https://www.broadinstitute.org/gatk/>). First, to determine the pathogenic variants for monogenic chylomicronemia, the exons of *LPL*, *APOC2*, *APOA5*, *LMF1* and *GPIHBP1* were investigated.

**Table 1. Results of Studies of Lipids, Apolipoproteins and Lipoprotein Lipase.**

	Patient	Mother	Reference range
TC	224	303 mg/dL	(150-219)
HDL-C	15	62 mg/dL	(Male, 40-86; Female, 40-96)
TG	2,524	147 mg/dL	(50-149)
LDL-C	45	195 mg/dL	(70-139)
ApoA-I	86	157 mg/dL	(Male, 119-155; Female, 126-165)
ApoA-II	20.6	35.9 mg/dL	(Male, 25.9-35.7; Female, 24.6-33.3)
ApoB	61	149 mg/dL	(Male, 73-109; Female, 66-101)
ApoC-II	10.6	7.0 mg/dL	(Male, 1.8-4.6; Female, 1.5-3.8)
ApoC-III	22.8	12.2 mg/dL	(Male, 5.8-10.0; Female, 5.4-9.0)
ApoE	9.7	6.5 mg/dL	(Male, 2.7-4.3; Female, 2.8-4.6)
LPL	undetectable	39 ng/mL	not determined
PHLPL	26	not measured ng/mL	(164-284)

Results of lipids, apolipoproteins and post heparin lipoprotein lipase mass are shown in columns with reference range in parenthesis. TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglyceride, LDL-C: low-density lipoprotein cholesterol, Apo: apolipoprotein, LPL: lipoprotein lipase, PHLPL: post-heparin lipoprotein lipase



**Figure 1.** A creamy layer on top with turbid infranatant was confirmed.

Secondly, *APOC3*, *ANGPTL3* and *ANGPTL4*, which encode proteins inhibiting LPL, were investigated. Thirdly, genotyping of *APOE* was performed. Lastly, heterozygous variants of *LDLR*, *APOB* and *PCSK9* were searched to evaluate whether the patient had a causative variant for familial hypercholesterolemia.

Two heterozygous variants of *LPL* discovered by whole exome sequencing were also confirmed by Sanger sequencing using recently described primers (forward primer 5'-TG ACAAGTGGTAGGTGGGTA-3' and reverse primer 5'-GGA AGAAAGAACAGCCGTT-3' for p.Tyr88X and forward primer 5'-TTACAAATCTGTGTTCCCTGC-3' and reverse primer 5'-GGGTCAATAAGGGTTAAGG-3' for p.Gly215 Glu) (5). After initial denaturation for 2 minutes at 98°C, a polymerase chain reaction was performed (35 cycles with 10

seconds at 98°C, 10 seconds at 58°C and 30 seconds at 68°C) using KOD SYBR qPCR Mix (TOYOBO, Osaka, Japan) on a StepOne Real-Time PCR system (Applied Biosystems, Foster City, USA).

### Family study

The family study only included the patient's mother, in whom a physical examination revealed no remarkable findings (including skin stigmata or Achilles' tendon thickening). The TC, TG, HDL-C, LDL-C, apoA-I, apoA-II, apoB, apoC-II, apoC-III, and apoE levels and pre-heparin LPL mass were measured and Sanger sequencing was performed using the same methods as were used for the patient.

### Ethics

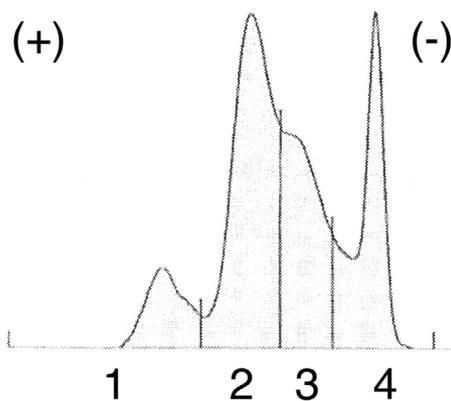
Genetic testing and other studies were performed in conformity with the Declaration of Helsinki and were approved by the Ethics Committee of Nihon University School of Medicine. Both the patient and his mother were fully informed of the procedures related to this study and provided their written consent.

### Results

Table 1 shows the results of studies of lipids, apolipoproteins and the pre- and post-heparin LPL mass. The patient had a markedly high TG value and low HDL-C and LDL-C values. Decreased apoA-I, apoA-II and apoB and increased apoC-II, apoC-III and apoE are compatible with the diagnostic criteria for primary chylomicronemia. No pre-heparin LPL mass was detected in the patient, indicating severe interference with LPL synthesis. The post-heparin LPL mass was not completely absent but was significantly lower than the reference range. The apoE phenotype was E3/E3. After the refrigerator test, the serum had a creamy layer on top with a turbid infranatant, indicating type V dyslipidemia according to the Fredrickson classification (Fig. 1). Type V dyslipidemia was also confirmed based on the patient's in-

creased pre-beta lipoprotein level, which corresponded to very low-density lipoprotein (VLDL), and chylomicrons presenting at the origin on agarose gel electrophoresis (Fig. 2). The mother had a high LDL-C value but her TG value was within normal range. Furthermore, the LDL-C/apoB ratio (1.31) did not indicate increased TG-rich lipoproteins, while the patient's LDL-C/apoB ratio was low (0.74). The apoC-II, apoC-III and apoE levels were also increased in the mother's serum, but were lower in comparison to those in the patient's serum. In comparison to the patient, the mother's pre-heparin LPL mass was relatively preserved. Fig. 3 shows a family tree based on lipid panels.

The quality of whole exome sequencing was sufficient (Table 2). On whole exome sequencing, two non-synonymous variants in *LPL* were discovered. One was het-



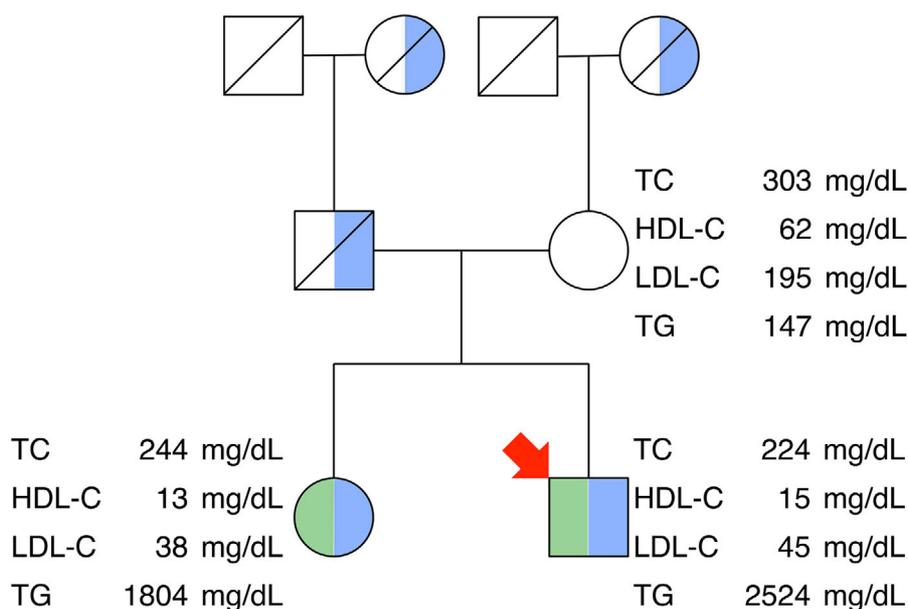
**Figure 2.** Agarose gel electrophoresis indicates fasting chylomicronemia with increased VLDL. Fraction 1, alpha lipoprotein. Fraction 2, pre-beta lipoprotein. Fraction 3, beta lipoprotein fraction. Fraction 4, the origin of the remaining lipoprotein. VLDL: very low-density lipoprotein

erozygous c.264T>A in exon 3, which introduced the stop codon p.Tyr88X; the other was heterozygous c.644G>A in exon 5, which indicated the amino acid change p.Gly215Glu. No non-synonymous or splice-site variants were detected in *APOC2*, *APOA5*, *LMF1*, *GPIHBP1*, *APOC3*, *ANGPTL3* and *ANGPTL4*. No variants, including p.Arg176Cys for the *APOE* 2 genotype, were found in the patient's *APOE*, denoting an E3/E3 genotype. While no heterozygous non-synonymous or splice-site variants were detected in *LDLR* or *APOB*, a heterozygous variant (p.Ala53Val) was detected in *PCSK9*. This was, however, classified as a benign variant for a Mendelian disorder according to the American College of Medical Genetics and Genomics because its allele frequency was shown to be as high as 9.6% in the Exome Sequencing Project (6). Additionally, this variant has been classified as benign/likely benign in ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>).

Sanger sequencing, which was subsequently performed confirmed the two heterozygous variants c.264T>A and c.644G>A of *LPL* in the patient's genome (Fig. 4). However, only c.644G>A in exon 5 causing p.Gly215Glu was confirmed in the mother's genome (Fig. 5). These results indicated that the patient's *LPL* carried trans-allelic heterozygous c.264T>A and heterozygous c.644G>A.

## Discussion

*LPL* is well known as a representative enzyme of lipolysis. To fulfill its enzymatic performance, however, *LPL* requires some co-factors: lipase maturation factor 1 (*LMF1*) encoded by *LMF1*, glycosylphosphatidylinositol anchored high-density lipoprotein binding protein 1 (*GPIHBP1*) encoded by *GPIHBP1*, apoC-II encoded by *APOC2* and apoA-V encoded by *APOA5*. In the lipolysis cascade, *LMF1* pro-



**Figure 3.** Squares, male; Circles, female; Diagonal line, deceased; Red arrow, index patient; Blue, hypertriglyceridemia; Green, chylomicronemia.

vides the homo-dimerization of LPL, then GPIHBP1 mediates the trans-endothelial transport of LPL and the anchoring of LPL to the capillary lumen (7). Thereafter, LPL hydrolyzes TG into TG-rich lipoproteins; that is, chylomicrons and VLDL, with the assistance of apoC-II and apoA-V (8, 9). Genetic etiology is an important factor in the development of primary chylomicronemia. Bi-allelic pathogenic variants of *LPL*, *APOC2*, *APOA5*, *LMF1* and

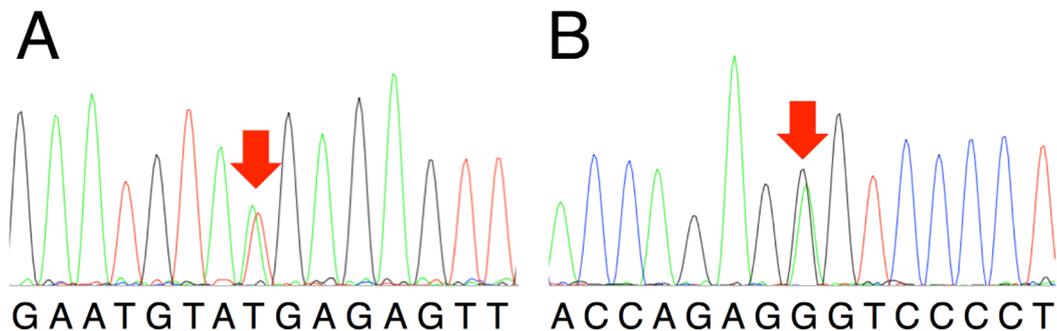
*GPIHBP1* are now widely accepted to be the primary cause of monogenic chylomicronemia (1). The following conditions typically arise in type I dyslipidemia: increased chylomicron and reduced VLDL and low-density lipoprotein and high-density lipoprotein (1). Monogenic chylomicronemia is most frequently caused by *LPL* variants and typically manifests as severe chylomicronemia from infancy or childhood (1). The *APOC2* variant is the second most frequent cause and results in severe chylomicronemia from childhood to adolescence (1). Cases due to *GPIHBP1*, *APOA5* and *LMF1* variants are rarer and are characterized by relatively mild chylomicronemia (1).

We reported a Japanese case of primary chylomicronemia in which a compound heterozygous p.Tyr88X and p.Gly215 Glu in *LPL* was the genetic etiology. Thus, the patient was diagnosed with LPL deficiency. In Japan, LPL deficiency has been reported in patients from more than 30 families. These cases typically exhibit the following phenotype: chylomicronemia resulting in markedly high serum TG values (1,500-20,000 mg/dL) beginning in early childhood; abdominal pain due to pancreatitis following fat intake; failure to thrive due to habitual avoidance of fat intake; hepatosplenomegaly due to infiltration of foam cells; and eruptive xanthoma and lipemia retinalis if serum TG levels exceed 2,000 and 4,000 mg/dL, respectively (3).

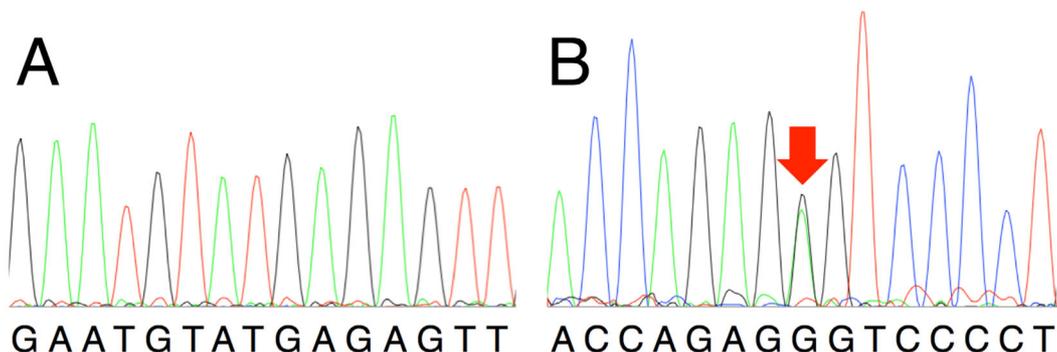
Recently, a large number of pathogenic variants in *LPL* for monogenic chylomicronemia have been reported. For in-

**Table 2. Whole Exome Sequencing Quality.**

Total read bases	12,368,772,696 bp
Total read bases	122,463,096
Q20	98.5 %
Q30	96 %
Mappable reads	122,360,024
%Mappable reads	99.9 %
Non-redundant reads	105,987,744
%Non-redundant reads	86.6 %
On-target reads	75,591,720
%On-target reads	71.3 %
Mean depth of target regions	102.4 X
%>1X	99.5 %
%>10X	89.5 %
%>20X	75 %
%>30X	63.5 %
%>50X	48.2 %



**Figure 4.** Results are shown with the reference base sequence. A red arrow indicates a variant. (A) Heterozygous c.264T>A was confirmed. (B) Heterozygous c.644G>A was confirmed.



**Figure 5.** Results are shown with the reference base sequence. A red arrow indicates a variant. (A) c.264T>A was not found. (B) Heterozygous c.644G>A was confirmed.

stance, 89 variants were enrolled as causative variants for LPL deficiency in the Human Genome Mutation Database (<http://www.hgmd.cf.ac.uk/ac/index.php>). Human LPL contains 475 amino acids, including a signal peptide consisting of 27 amino acids translated from 10 exons, and it is now widely accepted that most of the pathogenic variants are localized on exons 5 and 6 with some clustering because this area serves as a site for catalytic activity (3, 10, 11). However, the clinical manifestation of compound heterozygous p.Tyr88X and p.Gly215Glu in *LPL* remains to be described. In this present case, LPL protein could not be produced by the father's allele, which carried p.Tyr88X because nonsense-mediated decay was presumed based on a truncation located at exon 3 of the 10 exons (12). Indeed, a 3-month-old infant with a class 1 defect in LPL protein measured at 0 ng/mL due to homozygous p.Tyr88X was reported (13). The *LPL* variant p.Gly215Glu in the homozygous or compound heterozygous state is well known to be the most frequent cause of LPL deficiency in Europeans (11, 14). This variant has also been reported in Japanese individuals, and causes a class 2 defect resulting in a low (but not absent) LPL mass, despite severely impaired LPL activity (15-17). These reports support that compound heterozygous p.Tyr88X and p.Gly215Glu in *LPL* had a substantial impact on the development of LPL deficiency in the present case.

Although the key differential diagnoses of patients with hypertriglyceridemia and a family history of this condition include familial combined hyperlipidemia and familial dysbetalipoproteinemia, their presence was unlikely in this case. A high apoB level exceeding 120 mg/dL is known to be the best diagnostic predictor for familial combined hyperlipidemia; however, the serum apoB level in this patient was rather low (18). Similarly, the coexistence of a TG (mmol/L)/apoB (g/L) ratio of <10 and a TC (mmol/L) /apoB (g/L) ratio of >6.2 can identify familial dysbetalipoproteinemia with an area under the ROC curve value of 0.99; however, the TG/apoB ratio of 46.75 in the present patient clearly deviated from these criteria while the TC/apoB ratio of 9.51 was compatible (19). Additionally, the apoE phenotype and *APOE* genotype were unremarkable.

The results of the refrigerator test and agarose gel electrophoresis led to the condition being categorized as type V dyslipidemia according to the Fredrickson classification. These results are of interest because LPL deficiency generally indicates type I dyslipidemia and VLDL is not increased upon fasting. In type I dyslipidemia, chylomicron synthesized from dietary fat in intestinal cells is retained, even in fasting serum but VLDL is not increased. The key differential diagnoses of this type are congenital lipid disorders: LPL deficiency and apoC-II deficiency (3). Interestingly, while almost all TG is contained in the chylomicron region, a small amount of TG is found in the VLDL region of typical patients with LPL deficiency; however the reason for this is unclear (20). On the contrary, the disease spectrum of type V dyslipidemia covers a broad range of meta-

bolic disorders, including various genetic and environmental factors (1, 3). In addition to chylomicron, increased circulating VLDL in serum, which reflects endogenous overproduction from the liver or interfered lipolysis, is observed in this type (1, 3). Thus, type V dyslipidemia in this present case might result from the coincidence of metabolic syndrome and diabetes mellitus with insulin resistance, which causes increased VLDL production from the liver leading to elevated concentrations in serum. Several factors are involved in this overproduction of VLDL. First, the apoB pool, which is available for VLDL synthesis increases, microsomal triglyceride transfer proteins synthesizing VLDL increases, and the activities of ADP ribosylation factor 1 and phospholipase D1 - both of which involve VLDL trafficking - increase in liver if there is insulin resistance. The second factor is the increased flux of non-esterified fatty acids to the liver due to the weakened inhibition of hormone sensitive lipase, which leads to increased lipolysis in adipose tissue. The third factor is the activation of *de novo* lipogenesis because of the overexpression of carbohydrate responsive element-binding protein and sterol regulatory element-binding transcription factor 1c (21). In addition, the rate of VLDL production reflects the liver fat content and the severity of insulin resistance (22, 23). In Japanese patients with type 2 diabetes, the value of 20/(fasting C-peptide × fasting plasma glucose) has been reported to closely correlate with the glucose infusion rate, as determined by the glucose clamp technique. This is the gold standard method for evaluating insulin resistance; however, it is difficult to perform in clinical practice (24). Based on the regression equation in that report, the estimated glucose infusion rate in the present case was 4.68 mg/kg/min, which clearly showed the presence of insulin resistance. Once the VLDL increases in the serum, it may be difficult to remove because the severe interference with the lipolysis cascade in patients with LPL deficiency. This means that bi-allelic LPL pathogenic variants can be latent in type V dyslipidemia, and in such cases the genetic background of a defect in lipolysis will be unfailingly inherited in the next generation in comparison to the pattern of inheritance when the index patient has polygenic chylomicronemia due to a heterozygous LPL pathogenic variant, whereby there is a 50% chance that each child will be a carrier.

This report is associated with some limitations. The first limitation is that genetic testing of the patient's sister was not performed. Although it is improbable because of the childhood onset and co-occurrence of severe hypertriglyceridemia in the patient and his sister, in the present case, the possibility of *de-novo* p.Tyr88X cannot be completely denied. If *de-novo* p.Tyr88X occurs in an allele inherited from the mother, p.Gly215Glu would not result in phenotypic LPL deficiency, since the translation of LPL is truncated further upstream at residue 88 and this amino acid change will not be translated. Thus, both the patient and his sister were thought to have polygenic chylomicronemia. The analysis of the affected sibling pair would be required to determine the genetic background; however, genetic testing of

the sister was not possible. The second limitation is the masking of the natural lipolysis capacity in this patient due to the presence of diabetes mellitus. The lipid metabolism should be reevaluated once the glucose metabolism has completely normalized in order to assess the unexpected results of the refrigerator test and agarose gel electrophoresis. Last is lack of post-heparin LPL activity measurements. Since the post-heparin LPL mass is clearly correlated with LPL catalytic activity, the severe interference of the LPL catalytic activity in the present patient is presumed to have occurred because the markedly low level of his post-heparin LPL mass (25, 26). Nevertheless, to assess a catalytic defect due to p.Gly215Glu in detail, the post-heparin LPL activity should be evaluated and genotyping should be performed in a future study using samples from the patient, sister, the patient's mother and future offspring.

In summary, we reported the case of a Japanese man with LPL deficiency complicated by diabetes mellitus. Although type I dyslipidemia according to the Fredrickson classification is a typical finding in patients with LPL deficiency, increased VLDL with chylomicronemia—that is, type V dyslipidemia—was observed in the present case. This case should alert practitioners to the possibility of latent LPL deficiency in patients with type V dyslipidemia.

**The authors state that they have no Conflict of Interest (COI).**

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